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PATENT

Case Docket No. GENAPP.002RA
Date: November 5, 1999

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s)	:	T. Venkat Gopal
Appl. No.	:	09/404,979
Filed	:	September 22, 1999
For	:	PEPTIDE-MEDIATED GENE TRANSFER
Examiner	:	Unknown
Group Art Unit	:	~~1745~~

I hereby certify that this correspondence and all marked attachments are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on

November 5, 1999
(Date)

Nancy W. Vensko, Reg. No. 36,298

TRANSMITTAL LETTER

ASSISTANT COMMISSIONER FOR PATENTS
WASHINGTON, D.C. 20231
ATTENTION: APPLICATION BRANCH

Dear Sir:

Enclosed for filing in the above-identified application are:

(X) An Information Disclosure Statement.

(X) A PTO Form 1449 with One Hundred Twenty Eight (128) references.

(X) The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment, to Account No. 11-1410. A duplicate copy of this sheet is enclosed.

(X) Return prepaid postcard.

Nancy W. Vensko
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Attorney of Record

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GENAPP.002RA PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: T. Venkat Gopal	)
Application No.	: 09/404,979	)
Filed	: Sep. 22, 1999	)
Assignee	: Genetic Applications, LLC	)
For	: PEPTIDE-MEDIATED GENE TRANSFER	)

INFORMATION DISCLOSURE STATEMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

Enclosed is form PTO-1449 listing references that are also enclosed. While Applicant provides a brief statement of the relevance of the references considered to be most material to patentability, it is understood that the Examiner is not to rely on this statement as a comprehensive exposition of the relevance of those references nor on Applicant's conclusion that those references are most material to patentability. Instead, the PTO should make its own full and independent review.

U.S Patent No. 5,354,844 to Beug et al. entitled PROTEIN-POLYCATION CONJUGATES (issued Oct 11, 1994) describes an invention that relates to a system for transporting nucleic acids into the cell, which is effected by receptor-mediated endocytosis. Using a transferrin-polycation conjugate, a complex can be formed with the polyanionic nucleic acid. This complex is bound to the tranferrin receptor, which is highly regulated in growing cells, and absorbed into the cell.

Garcia-Bustos et al., Nuclear Protein Localization, Biochim. Biophys. Acta 1071:83 (1991) reviews the experimental approaches, findings and conclusions that have shaped the

understanding of nuclear protein localization and nuclear protein transport, which are mediated by a nuclear localization signal (NLS).

N. Raikhel, Nuclear Targeting in Plants, Plant Physiol. 100:1627 (1992) describes several types of nuclear localization signals that have been identified in plants.

Kaneda et al., Increased Expression of DNA Cointroduced with Nuclear Protein in Adult Rat Liver, Science 243:375 (1989) describes DNA and nuclear proteins that were transferred into cells simultaneously at more than 95% efficiency by means of vesicle complexes.

WO93/19768 (published Oct 14, 1993) and corresponding U.S. Patent No. 5,955,365 to Szoka et al. entitled SELF-ASSEMBLING POLYNUCLEOTIDE DELIVERY SYSTEM (issued Sep 21, 1999) describes an invention that provides a self-assembling polynucleotide delivery system comprising components aiding in the delivery of the polynucleotide to the desired address which are associated via noncovalent interactions with the polynucleotide. The components of this system include DNA-masking components, cell recognition components, charge-neutralization and membrane-permeabilization components, and subcellular localization components. Specific compounds are also provided.

Morin et al., Nuclear Localization of the Adenovirus DNA-Binding Protein: Requirement for Two Signals and Complementation during Viral Infection, Mol Cell Biol 9:4372 (1989) describes the adenovirus DNA-binding protein (DBP) that is an abundant multifunctional protein located primarily in the nuclei of infected cells. To define sequences involved in nuclear transport of DBP, a series of point and small deletion mutants were constructed via oligonucleotide-directed mutagenesis. Two short stretches of basic amino acids located in the amino-terminal domain (amino acids 42 to 46 and 84 to 89) were identified. A nuclear localization defect could be complemented by viral infection.

Jenster et al., Nuclear Import of the Human Androgen Receptor, Biochem J 293:761 (1993) describes the nuclear import of the human androgen receptor that was investigated by immunocytochemical analysis of androgen receptor deletion and substitution mutants, which were transiently expressed in COS-1 cells. The signal responsible for nuclear import is encoded by amino acids 608-625 and is functionally similar to the bipartite nucleoplasmin nuclear-localization signal.

A. Van Der Krol and N. Chua, The Basis Domain of Plant B-ZIP Proteins Facilitates Import of a Receptor Protein into Plant Nuclei, Plant Cell 3:667 (1991) describes testing several

basic domains from plant DNA-binding proteins for nuclear targeting function. When tested as N-terminal fusions to the β-glucuronidase protein, only those constructs containing the DNA binding (basic) domain of the basic-zipper (B-ZIP) region conferred nuclear import, suggesting a close association or overlap of the DNA binding and nuclear targeting domains of B-ZIP proteins. Additional studies suggested a strong correlation between nuclear import mechanisms in animals and plants.

Matheny et al., The Nuclear Localization Signal of NGF-1A Is Located within the Zinc Finger DNA Binding Domain, J Biol Chem 269:8176 (1984) describes NGF-1A that is an immediate-early gene that encodes a transcription factor whose DNA binding domain is composed of three zinc fingers. To identify its nuclear localization signal (NLS), wild type NGF-1A and various mutants were transfected into COS cells and their cellular localization assayed by indirect immunofluorescence. Although wild type NGF-1A was located exclusively in the nucleus, deletions lacking the highly basic zinc finger region were not efficiently translocated to the nucleus. To determine the minimal region(s) of NGF-1A sufficient to direct nuclear localization, the cellular location of various NGF-1A/β-galactosidase fusion proteins was examined. The studies suggested that NGF-1A contains a novel NLS that is dependent on the overall structure of the DNA binding domain and not solely upon its highly basic nature.

Schreiber et al., The Human Poly (ADP-ribose) Polymerase Nuclear Localization Signal Is a Bipartite Element Functionally Separate from DNA Binding and Catalytic Activity, EMBO 11:3263 (1992) describes Poly (ADP-ribose) polymerase (PARP) that is a zinc finger DNA-binding protein involved in DNA repair processes in eukaryotes. By deletion and extension site-directed mutagenesis, its DNA-binding domain fused to the N-terminus of β-galactosidase was shown to contain a nuclear localization signal (NLS) of the form KRK-X(11)-KKKSKK (residues 207-226). The results presented here support the concept that the human PARP NLS is an autonomous functional element and belongs to the class of bipartite NLSs.

This Information Disclosure Statement is being filed within three months of the filing date of this reissue application, and no fee is required in accordance with 37 C.F.R. § 1.97(b)(1).

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 11/5/99

By: _____

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